

REMARKS

The Invention

Biodegradable macromers, such as those described in U.S. Patent No. 5,410,016, have been developed for the sustained delivery of biologically active substances (BAS). These sustained released systems can result in rapid initial rates of release (burst) and insufficient bioavailability of the BAS over time. The present invention decreases burst and improves bioavailability as a result of formulating the BAS in an insoluble form within the biodegradable macromer. This is accomplished by addition of a molecule or mixture of molecules which reduces the solubility of the BAS during the manufacturing process of the therapeutic article to less than 10 mg/ml.

Rejection for Double Patenting

Claims 1-10 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 10, 25, 28, 29, and 49-54 of U.S. Patent No. 6,699,504.

Applicants have addressed the double patenting rejection by disclaiming the terminal portion of the term of the entire patent to be granted upon the application subsequent to the expiration date of U.S. Patent No. 6,699,504. In view of this disclaimer, Applicants request withdrawal of the double patenting rejection.

Rejection under 35 U.S.C. § 102

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,410,016 to Hubbell et al. (hereafter “Hubbell ‘016”).

Applicants have addressed this rejection by amendment of claim 1, and claims 2-5 dependent thereto, to require that the molecule or mixture of molecules which preferentially excludes proteins be present in an amount sufficient to reduce the solubility of the biologically active substance to less than 10 mg/ml. Applicants note that Hubbell ‘016 does not teach the use of a molecule or mixture of molecules present in quantities sufficient to reduce the solubility of a biologically active substance to less than 10 mg/ml.

In view of this amendment, Applicants request withdrawal of the anticipation rejection.

Support for the amendments to the claims

Claim 1 has been amended to recite that “said molecule or mixture of molecules is present in an amount sufficient to reduce the solubility of said human growth hormone in said article to less than 10 mg/ml.” Support for this amendment is found in the specification at page 8, lines 8-15, in the definition of a molecule or mixture of molecules that preferentially excludes proteins. Claim 1 has also been amended to recite an article containing precipitated human growth hormone. Support for this amendment is found in the specification at page 24, lines 4-24; in FIG. 1, which depicts the release profile of microspheres made with precipitated hGH; and in Example 2 at page 39, line 14, to page

40, line 3, which describes the precipitation of hGH by the addition of PEG 2K.

Support for an article comprising 5% or 10% active substance, as recited in claims 10 and 11, respectively, is found in the specification at page 6, lines 12-15.

Support for a molecule or mixture of molecules present in an amount sufficient to reduce the solubility in said article to less than 1 mg/ml, as recited in claim 12, is found in the specification at page 8, lines 8-15.

Support for the release profiles recited in claims 13 and 14 is found in the specification from page 2, line 20, to page 3, line 3.

Support for the release profile recited in claim 15 is found in the specification at page 7, lines 15-16.

Support for an article having a particle size of less than 75 microns, as recited in claim 16, is found in the specification at page 22, lines 18-21.

Support for a water soluble region comprising poly(ethylene glycol) of about 500 to 20,000 daltons, as recited in claim 17, is found in the specification from page 23, line 23, to page 24, line 2.

Support for a molecule or mixture of molecules comprising a positively charged ion-carrying reagent, as recited in claim 18, a negatively charged ion-carrying reagent, as recited in claim 19, and a surfactant, as recited in claim 20, is found in the specification at page 3, lines 11-19.

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for 3 months, to and including Monday January 24, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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